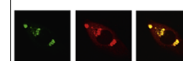


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Research Report

Features and timing of the response of single neurons to novelty in the substantia nigra



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ABSTRACT

Substantia nigra neurons are known to play a key role in normal cognitive processes and disease states. While animal models and neuroimaging studies link dopamine neurons to novelty detection, this has not been demonstrated electrophysiologically in humans. We used single neuron extracellular recordings in awake human subjects undergoing surgery for Parkinson disease to characterize the features and timing of this response in the substantia nigra. We recorded 49 neurons in the substantia nigra. Using an auditory oddball task, we showed that they fired more rapidly following novel sounds than repetitive tones. The response was biphasic with peaks at approximately 250 ms, comparable to that described in primate studies, and a second peak at 500 ms. This response was primarily driven by slower firing neurons as firing rate was inversely correlated to novelty response. Our data provide human validation of the purported role of dopamine neurons in novelty detection and suggest modifications to proposed models of novelty detection circuitry.

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1. Introduction

It is well-established in animal models and neuroimaging studies that substantia nigra (SN) neurons, especially dopamine (DA) neurons, avidly respond to reward (Hollerman and Schultz, 1998) as well as novelty (Bunzeck and Düzcel, 2006; Legault and Wise, 2001; Li et al., 2003; Ljungberg et al., 1992).

A consensus has formed that both increases and decreases in DA neuron firing rate serve as learning signals (Schultz, 2007); a large phasic increase in DA from the SN/ventral tegmental area (VTA) to the nucleus accumbens likely strengthens hippocampal inputs when reward is located, leading to memory reinforcement of rewarded behaviors (Goto and Grace, 2005). These observations have led to the hypothesis

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that DA signaling is required for late long-term potentiation (LTP). Some predictions of this model have been confirmed by neuroimaging studies; notably, reward representations in the striatum appear to be enhanced by preceding novel scenes (Guitart-Masip et al., 2010), and memory for visual scenes at 24 h after an fMRI experiment correlated to activation within the hippocampus, ventral striatum, and SN/VTA (Bunzeck et al., 2012). However, human electrophysiology studies have not been performed to test key parts of this hypothesis.

Specifically, the timing of the substantia nigra response to novelty is unknown; a popular model predicts an early response to novelty, which serves to strengthen hippocampal synapses formed during behaviorally salient novel events (Lisman et al., 2011). Primate studies have also supported a very short latency (~100 ms) for phasic DA responses to novel stimuli (Ljungberg et al., 1992), but some longer-latency responses have been observed, on the order of 200 ms (Mireniewicz and Schultz, 1994). However, with some authors positing a “systems-wide computation...[to determine] that there is a high level of novelty or motivational salience” as a requirement for DA release (Lisman et al., 2011), it is critical to know when precisely this release occurs. Using event-related potentials in patients implanted with externalized DBS electrodes, novel stimuli were associated with both an early hippocampal peak (~180 ms) and a late nucleus accumbens peak (~480 ms) that was correlated to increased retention in memory (Axmacher et al., 2010). However, this study did not directly address the midbrain. The authors posit that the link between the hippocampal activation and the nucleus accumbens activation is the dopamine system; we used a novelty-oddball task to detect the posited early substantia nigra response that would conform to this hypothesis, as well as to characterize its features and timing, to a degree not possible with fMRI. This task is also used in electroencephalography (EEG) experiments to evoke the novelty P300, a hippocampally-dependent event related EEG potential (Knight, 1996) (Fig. 1).

2. Results

Forty-nine putative neurons were identified. A total of 14959 standard trials, 912 target trials, and 1249 novel sound trials were performed. Novel sounds evoked a greater response compared to standard tones over the 250–350 ms interval ($F_{\text{stimulus}}=6.9$, $p=0.010$ (250–300 ms) and $F_{\text{stimulus}}=7.1$, $p=0.009$ (300–350 ms), $p=0.037$ (both intervals) after correction for multiple comparisons by FDR, Fig. 2). A second peak of significantly increased firing was seen from 500 to 600 ms ($F_{\text{stimulus}}=7.1$, $p=0.009$ (500–550 ms) and $F_{\text{stimulus}}=7.8$, $p=0.006$ (550–600 ms), $p=0.037$ (both intervals) after correction for multiple comparisons by FDR). Responses to target tones and standard tones did not significantly differ over any interval. The aggregated normalized firing rate following all standard tone and novel sound trials is displayed in Fig. 2, which shows a peak beginning approximately 250 ms following novel sounds, and reaching its zenith at 300 ms. A second peak was seen beginning at 500 ms.

To confirm that substantia nigra neurons differentiated standard and novel tones, we performed principal

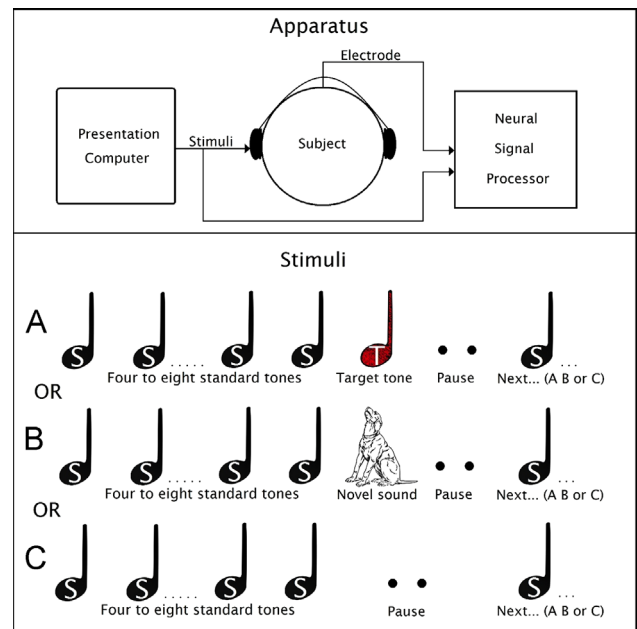


Fig. 1 – Apparatus and Task. The apparatus consisted of a presentation computer, headphones, a microelectrode, and a neural signal processor. We used a variation on the novelty P300 task as described by Fabiani and Friedman (1995) and Knight (1996) to study midbrain responses to stimuli. Novel sounds included environmental sounds (animal noises), mechanical sounds, or non-standard, non-target musical tones.

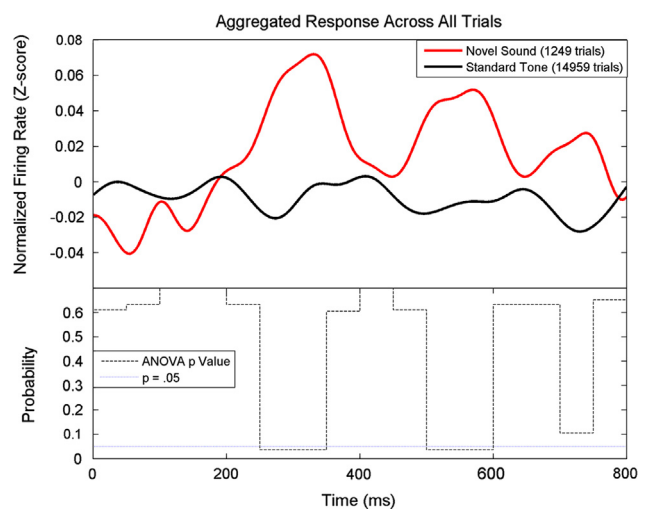


Fig. 2 – Aggregated Neuron Responses. The smoothed normalized firing rate was calculated at each millisecond for each trial as described in the text. The curves here depict the average firing rate across all novel trials (red) and all standard trials (black).

component analysis (PCA) on the 800 ms following the stimulus for responses to standard and novel tones. The population of neurons recorded was heterogenous, and not all neurons were expected to discriminate novels and standards. Furthermore, stimulus novelty seems likely to be only

one of many sources of variance within the firing rate of neurons in the SN (other sources could be reward predication error (Hollerman and Schultz, 1998) or relevance as a learning signal (Ljungberg et al., 1992), factors that the present experiment is not designed to quantify). We therefore used PCA to quantify how discriminatory each neuron was, in terms of stimulus novelty. These analyses were performed in addition to, not instead of, analysis of the original data (Fig. 2). As stated in the Section 5, the top three components captured 56.9% of variation across all neurons, and were used for this analysis. Two-sample T-tests were performed comparing principal component scores for novel versus standard stimuli for 49 cells over three components (see Section 5); this yielded three tests per neuron, with each neuron having a 14.3% probability of having at least one significant component by chance alone. 13 Of 49 neurons showed at least one component which significantly differentiated standards and novels (versus 7 expected, $p=0.014$ by Chi square). We then averaged

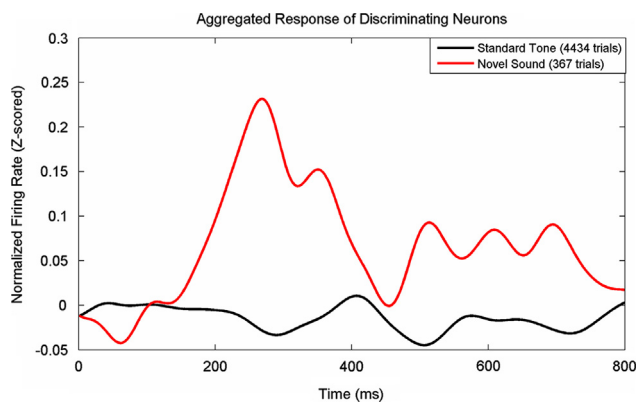


Fig. 3 – Averaged PCA of discriminating neurons. PCA was performed for 49 neurons, yielding 13 neurons that differentiated standard and novel tones. An increase in firing rate was noted for novel tones in discriminatory neurons at peaks similar to those described in the aggregate response.

PCA components of these 13 neurons; two peaks were seen, at 300 ms and 500 ms, similar to the averaged responses (Fig. 3). The waveforms and activity of two typical cells of this group are shown in Fig. 4. The mean firing rate of this population was 7.93 spikes/s, whereas the firing rate of non-discriminatory neurons was 13.6, though this did not meet statistical significance. We therefore investigated how firing rate differentiated response to standard and novel tones.

As stated above, the PCA analysis suggested slower-firing cells might respond to novelty more than faster neurons. We thus investigated the fastest firing subset of our population (neurons with firing rates from 18.5 to 55.0 spikes/s). We thought they might represent GABA-ergic interneurons found within the SN, which have firing rates between 15 and 100 spikes/s, and are known to have an inhibitory effect on local DA neurons (Tepper et al., 1995). The twelve fastest-firing neurons were suppressed by novel stimuli (Wilcoxon rank-sum, $p<0.05$). This effect was no longer significant if we included the next-slowest neuron in the analysis, but it was significant for any faster cutoff selected (e.g., the fastest eleven, ten, or nine neurons). All neurons in this subgroup demonstrated decreased activity between 250 and 350 ms following novel stimuli. To further investigate the relationship between firing rate and novelty response, we compared firing rate to novelty response across all 49 neurons. Overall neuron firing rate was significantly anti-correlated with the mean normalized firing rates during this interval ($r=-0.34$, $p=0.018$, Fig. 5), suggesting a slower sub-population of neurons was responsible for the overall trend toward increased activity at 300 ms following novel stimuli, and faster neurons were responsible for suppression of firing.

3. Discussion

The increased SN neuron activity following novel sounds compared to standard and target tones demonstrates that SN activity does occur in the setting of auditory novelty in

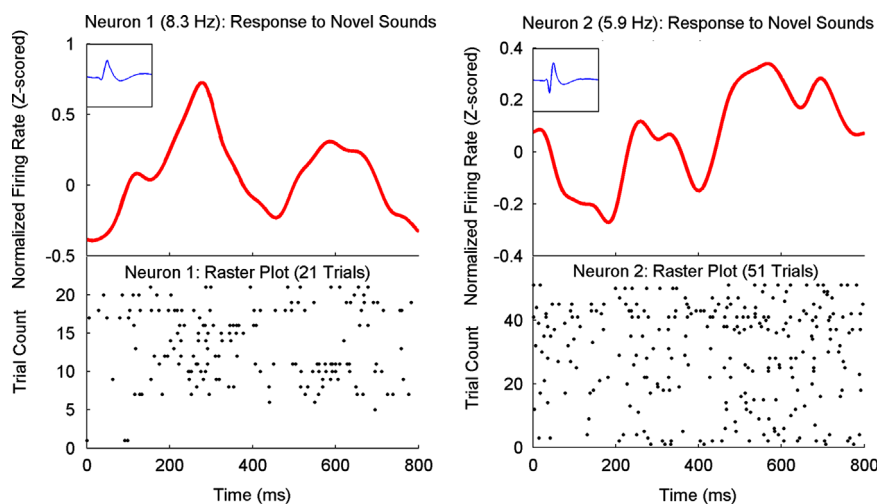


Fig. 4 – Example neurons. The normalized firing rates over novel sound trials (red) and standard tone trials (black) are depicted for two individual neurons in the top panels of this figure. These smoothed rates were calculated in the same manner as in Fig. 2. The waveforms of the two neurons are depicted in the top-left insets in blue.

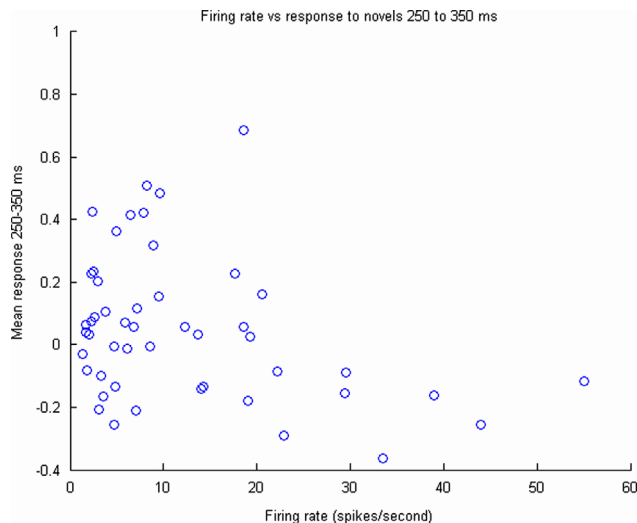


Fig. 5 – Firing rate versus response to novels. Z-scored firing rate (Y-axis) is compared to firing rate (X-axis). The eight fastest neurons decrease their firing rate in response to novel stimuli, and there is a negative correlation between firing rate and novelty response, suggesting that different populations of neurons respond differently to novelty within the substantia nigra.

humans. The neuron firing rate increased 250–350 ms after stimulus onset, concurrently with the onset of hippocampally-dependent novelty P300 in the cortex, and well after novelty-response hippocampal activity has been shown to begin (<100 ms after stimulus onset) with a similar auditory task in animal models (Ljungberg et al., 1992; Ruusuvirta et al., 1995). Additionally, we found evidence for a later signal from (500–600 ms) that might signal behavioral salience back to the hippocampus in accordance with the predictions of the neo-Hebbian model proposed by Lisman et al., (2011). Further experimentation will be required to verify this possibility. We speculate that slower-firing units that respond to novelty are dopaminergic in character, whereas faster firing units suppressed by novelty (>20 Hz) may be tonically inhibitory interneurons within the SN (Grace and Bunney, 1980; Grace and Onn, 1989; Tepper et al., 1995).

Numerous other brain regions are involved in novelty detection, including the prefrontal cortex, thalamus, and primary sensory cortices (Gur et al., 2007). Dorsolateral prefrontal cortex (DLPFC), in particular, appears to be important for generation of the novelty p3 EEG potential (Lovstad et al., 2012). Nucleus accumbens (NAc) is also an important downstream target of the novelty response; DA responses detected in the shell subregion of the NAc appear to code an integrated signal of novelty and appetitive valence in rodents, and are rapidly habituated with repeated stimulus presentations (Bassareo et al., 2002). These data support the view that the novelty response is important in coding behavioral relevance that mark stimuli as critical for retention in long-term memory (Lisman et al., 2011). This view is consistent with recent findings reported by Zaghoul and colleagues, in which substantia nigra neuron firing reflected unexpected financial rewards, presumably of high behavioral relevance (Zaghoul et al., 2009a). In all cases, DA likely serves as a signal that the

stimulus may have great importance to the organism, and it effects downstream changes consistent with this.

Ours is the first report of neuron activation to non-reward-associated novelty in humans. While the primate literature on the subject is almost twenty years old, present models have not fully accounted for the relationship between novelty and reward. One theory suggests that the avidity of DA neuron firing in response to novelty depends heavily upon contextual cues suggesting that novelty is highly predictive of reward (Bunzeck et al., 2012). Latency of cortical activation has been seen to be as early as 85 ms when novelty is predictive of reward (Bunzeck et al., 2009). However, this seems like a highly artificial situation; in everyday life stimuli likely require extensive evaluation before it is knowable whether they predict reward. In this case the latency seen by Axmacher of ~480 ms of activation in the nucleus accumbens seems more plausible (Axmacher et al., 2010); the signal we have seen may represent the posited link between early hippocampal activation and later nucleus accumbens activation.

As mentioned in the introduction, we are mindful of literature describing latencies of 100–200 ms for onset of DA neuron firing to unconditioned stimuli. The somewhat later onset we describe may be a result of Parkinson pathophysiology; ERP studies have described lengthening of the onset of the novelty P3 potential to 400 ms in PD patients (Tsuchiya et al., 2000). Alternately, the larger brains of humans relative to both non-human primates and rodents may perform a significantly more nuanced evaluation of stimuli to determine novelty relative to other mammals; this corresponds to the “systems-wide computation” required for novelty detection posited by Lisman (Lisman et al., 2011). This computation no doubt involves multiple cortical and subcortical areas.

We are mindful that our analysis may have captured some non-DA units in the substantia nigra. This is an intrinsic limitation of extracellular recording in behaving human subjects, given technical and humane constraints on recording in the operating room. Additionally, Parkinson disease may have resulted in some loss of DA neurons in this population. However, DA neurons subserving cognitive processes such as novelty detection are thought to be lost late in the disease process (Gonzalez-Hernandez et al., 2010), and prior reports have described DA-like neurons during DBS surgery (Zaghoul et al., 2009b). The observed group effects are highly robust, and a number of the units met criteria for DA neurons. Our analysis is fine-grained enough to provide electrophysiological verification of neuroimaging findings that suggests a response to novelty in the midbrain, as well as information about the timing of this response. Such electrophysiological investigations into subcortical structures will provide critical information for the development of models of substantia nigra function.

4. Conclusion

Using neurophysiological techniques, we have shown that the human substantia nigra encodes novelty. The timecourse of this encoding is biphasic with peaks at 250 and 500 ms. These data support the view that SN activation is associated

with both an early phasic signal and a later signal, possibly associated with incorporation of the sensory trace into long-term memory. To understand how SN function contributes to behavior, further experiments will be required to characterize the response properties of this critical structure.

5. Experimental procedures

5.1. Subjects

Patients with Parkinson disease who were considered candidates for surgical therapy were approached for participation in the study. To be considered surgical candidates, patients had to be free of major neurological comorbidities (e.g., Parkinson's-plus) syndromes, including dementia. Ten patients with a mean age of 65 ± 9.0 years and mean disease duration of 12.5 ± 4.1 years were enrolled according to a protocol approved by the Columbia University Medical Center Institutional Review Board (CUMC IRB).

5.2. Ethics statement

All study procedures were conducted with CUMC IRB approval in accordance with state and federal guidelines. All patients provided informed consent. Following discussion of the study, questions were answered and a copy of the consent form was given to the patient. Consent discussions were documented by study personnel. The CUMC IRB approved all consent and human experimentation procedures in this study.

5.3. Microelectrode recording

Microelectrode recordings were carried out with paired 1- μ M tungsten-tip electrodes with a power-assisted microdrive. A neural signal processor (Cerberus™ from Blackrock Microsystems, Salt Lake City) recorded from the microelectrode at 30 kilosamples/s. The auditory output of the presentation computer was recorded by the neural signal processor to allow for accurate comparison of stimulus times and neural activity. The substantia nigra was identified in accordance with guidelines from Hutchinson et al., (1998).

5.4. Behavioral task

During recording of the substantia nigra for clinical purposes, using an auditory oddball methodology similar to that of Knight (1996), subjects were instructed to listen for rarely-repeated “target” tones in a series of repetitive standard tones and non-repeated novel sounds. The pattern of stimuli consisted of four to eight repetitive “standard” tones occurring every 800 ms followed by a “target” tone or a non-target non-repeated “novel” sound (e.g. canine bark; Fig. 1). Each stimulus was 336 ms in length. A pause of random duration between 2 and 4 s followed to jitter the stimuli, and then the pattern was repeated. The subjects were asked to count the target tones. In a version of the task used with five patients, approximately half of the target tones were replaced by silence, trials which are not considered here. This was done to perform a related experiment; access to the human midbrain is a scarce

resource and as many experiments as possible should be done as can be performed safely. Across all recording sessions, 5.3% of the stimuli were target tones, 7.3% of the stimuli were novel sounds, and the rest were standard tones.

5.5. Spike sorting

The recorded microelectrode signals were analyzed offline. A clustering algorithm (Wave Clus, Leicester, UK) was used to detect neural spikes and sort them into clusters representing putative neurons (Quiroga et al., 2004). Neurons were included for further analysis if there were at least 400 spikes recorded and ten novel sound trials performed. Because of the paired electrode tip and spike-sorting, multiple neurons were sometimes recorded simultaneously, and activity was measured for each neuron recorded during each stimulus.

5.6. Analysis of responses

To quantify the response of each neuron to each stimulus (i.e. the response for each trial), the instantaneous firing rate was calculated for each millisecond by convoluting the neuron spike histogram with a Gaussian kernel ($\sigma = 25$ ms). Responses were examined for the 800 ms following each stimulus. This firing rate curve was then normalized by subtracting the mean firing rate from the 10 s prior to stimulus onset and dividing by the standard deviation of the entire recording. We chose to divide by the standard deviation of the entire recording rather than the previous 10 s to avoid dividing by zero during periods of low neuron activity. We examined the hypothesis that novel stimuli would evoke a greater response from the neurons than repetitive stimuli using a method similar to Zaghoul et al., (2009a). A 2-way ANOVA was performed on all of the trial responses from all neurons, with stimulus type (novel vs. standard) as a fixed effect, and the recorded neuron as a random effect. This was performed on sixteen 50 ms bins from 0 to 800 ms, and again was repeated for the case of target vs. standard stimuli. We corrected for multiple comparisons using the false discovery rate (FDR) method. Most analysis was performed in Matlab (Mathworks, Natick, MA) but FDR was calculated using SAS (SAS Institute, Cary, NC).

5.7. Principal component analysis for evaluation of single neurons

Because clinical considerations limit the number of trials which could be performed while recording any single neuron, we opted to limit the number of comparisons in our examination of single neuron responses by using principal component analysis. Using the *princomp* command in Matlab, we transformed the 800 ms response curves following all trials for a given neuron into principal component space. This technique accounts for covariation within a neuron's trial response curves, reorganizing these 800 dimensional vectors into principal components, a small number of which can account for the vast majority of data variation. Each principal component is an 800 ms timeseries, and each trial has a score for each component such that the original trial response curve could be reconstructed by summing the products of

that trial's scores with their respective components. Components are ranked according to how much data variation they capture; in this case, the first component accounted for 31.1% of variance, the second for 14.5%, the third for 11.2%, and the fourth and fifth for 7.9% and 6.5%, respectively. Given that the top three components accounted for 56.9% of the variance, they were retained for further analysis, allowing us to capture the majority of data variation in only three dimensions, and thus reducing multiple comparisons. We therefore limited our analysis to these three components, comparing the scores for novel sounds with those of standard tones by means of two-sample *t*-test. Principal component analysis and the subsequent *t*-tests were repeated for every neuron. We then compared the number of discriminatory components we found to what would be expected by chance using a chi square test. Neurons with a component which successfully discriminated between stimulus types were examined further.

Author contributions

C.B.M., C.A.S., and G.M.M. designed research. C.B.M., J.P.S., B.E.Y., R.A.M., T.J.W., A.K.C., S.L.P., Q.Y., R.R.G., performed research. C.B.M., J.P.S., C.A.S., and G.M.M. analyzed data. C.B.M., J.P.S., A.K.C., and G.M.M. wrote the paper.

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